

**REMARKS**

Claims 1-7, 9, 10, 12, 14 and 15 are pending. Claims 11, 13, and 16-32 are canceled. By this amendment, claims 1, 4 and 7 are amended.

The amendments submitted after Final Office Action are for the purpose of presenting the rejected claims in better form for appeal. Applicants submit that the amendments do not raise new issues, do not require any further consideration or search by the Examiner and overcome all grounds of final rejection. Entry of the amendments are respectfully requested.

Amendment and cancellation of certain claim limitations are not to be construed as a dedication to the public of any of the subject matter of the claims as previously presented. Applicants reserve the right to pursue the amended and cancelled claims in a future continuation or divisional application.

Reconsideration of the application is respectfully requested in view of the above amendments and the following remarks. For the Examiner's convenience, Applicant's remarks are presented in the order in which they were raised in the Office Action.

**A. Deletion of the term "prophylactically"**

The term "prophylactically" has been removed from claims 1, 2, 4, and 7 according to the Examiner's suggestion. No new matter is added as the Examiner considers "inhibiting and inhibits" to have the same effect.

**B. Claim rejections under 35 U.S.C. § 102(b)**

Claims 1-7, 9, 11 and 12 stand rejected under 35 U.S.C. § 102(b) over Asmar *et al.* ("Asmar I") which is cited for teaching the treatment of type 2 diabetes and associated complications such as hypertension.

In response, Applicants amend claims 1, 4 and 7 to delete claim limitations that recite the use of telmisartan for treatment of a disease or condition.

For consideration by the Examiner, Applicants submit a copy of the scientific publication corresponding to the Asmar abstract. Asmar *et al.* Journal of the Renin-Angiotensin-Aldosterone System. 3(3):176-180 (September 2002); ("Asmar II") copy enclosed. The trial described in this Asmar II publication did not have diabetes as a primary or secondary endpoint as disclosed on page 177 under "Study endpoints." Instead the study relates to determination of a primary efficacy endpoint related to changes in pulse wave velocity (PWV). (Asmar II, page 177). PWV is a measure of arterial stiffness which is described as "an independent risk factor for cardiovascular mortality in hypertensive patients [and] is associated with atherosclerosis and is exacerbated in Type 2 diabetes." (Asmar II, page 176; citations omitted). Therefore, one of skill in the art would interpret Asmar II as teaching the inhibition of arterial stiffness in diabetes patients with essential hypertension, and not for teaching treatment, inhibition, slowing or delay of diabetes. Arterial stiffness is a risk factor for cardiovascular mortality independent from diabetes. The condition may be exacerbated in diabetes but is not disclosed by Asmar II as being dependent on diabetes.

Applicants further amend claims 1, 4 and 7 to specify use of telmisartan to inhibit, slow, or delay development of "at least one metabolic disorder or disease selected from the group consisting of insulin resistance, glucose intolerance, impaired glucose tolerance, impaired fasting serum glucose, impaired fasting blood glucose, hyperinsulinemia, pre-diabetes, type 1 diabetes, type 2 diabetes mellitus, insulin resistant hypertension, the metabolic syndrome, the metabolic hypertensive syndrome, (metabolic) syndrome X, the dysmetabolic syndrome, obesity, visceral obesity, and hypertriglyceridemia"

Applicants submit that to inhibit, slow, or delay development of a condition is not anticipated by Asmar as these limitations relate to administration of telmisartan to a population not (yet) suffering from these conditions and therefore are not inherently anticipated by Asmar which teaches administration of telmisartan to diabetes patients.

No new matter is added by these amendments which recite the limitation of the conditions for which telmisartan is used to inhibit, slow, or delay development. Support is found in the originally filed claims and throughout the specification.

In view of the amendments, Applicants respectfully request withdrawal of their ground for rejection under 35 U.S.C. § 102(b).

**C. Claim rejections under 35 U.S.C. § 103(a)**

Claims 10, 14 and 15 stand rejected under 35 U.S.C. § 103(a) over Asmar *et al.* which is cited for inherently teaching the treatment of metabolic hypertensive syndrome and type 2 diabetes, and the topical administration and dosage limitations of claims 10, 14 and 15 being obvious modifications.

As discussed above, claims 1, 4 and 7, as amended, are not (inherently) anticipated by Asmar. Claims 10, 14 and 15 depend from claim 1. Because all limitations of claims 10, 14 and 15 are not taught or suggested by Asmar, Applicants respectfully request withdrawal of this ground for rejection.

**CONCLUSION**

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to allow this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 421842000400. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: June 30, 2006

Respectfully submitted,

By 

Shantanu Basu

Registration No.: 43,318

MORRISON & FOERSTER LLP

755 Page Mill Road

Palo Alto, California 94304-1018

(650) 813-5995

**Keywords:**  
telmisartan,  
diabetes,  
hypertension,  
pulse wave  
velocity,  
stiffness,  
blood pressure,  
angiotensin II  
receptor blocker,  
pulse pressure

\* The Cardiovascular  
Institute, Paris, France  
† Hôpital St André,  
Bordeaux, France  
‡ GlaxoSmithKline,  
Greenford, UK

Correspondence to:  
Professor Roland  
Asmar  
The Cardiovascular  
Institute,  
21 Boulevard Delessert,  
75016 Paris,  
France  
Tel: +33 1 5574 6666  
Fax: +33 1 5574 6665  
E-mail: ra@icv.org

Accepted for  
publication  
30th September 2002

JRAAS 2002;3:176-80

**Journal of  
the Renin-  
Angiotensin-  
Aldosterone  
System**  
(Including other  
peptidergic systems)

September 2002  
Volume 3  
Number 3

## Effects of telmisartan on arterial stiffness in Type 2 diabetes patients with essential hypertension

Roland Asmar,\* Phillipe Gosse,<sup>†</sup> Jirar Topouchian,\* Gilbert N'tela,<sup>‡</sup> Amanda Dudley,<sup>‡</sup>  
Gillian L Shepherd<sup>‡</sup>

### Abstract

Arterial wall stiffness, an important independent risk factor for cardiovascular disease in patients with hypertension, is worsened by the coexistence of diabetes mellitus. This randomised, prospective, double-blind, crossover trial assessed the effects of telmisartan on arterial stiffness in patients with Type 2 diabetes with essential hypertension. After a two-week placebo wash out period, 28 ambulatory patients received telmisartan (40 mg) or placebo for three weeks. Following a second two-week placebo wash out period, patients received the alternate treatment for a further three weeks. Augmentation index and central blood pressure (BP) were determined using the SphygmoCor™ device and pulse wave velocity (PWV) was measured using an automatic device, the Complior™, at the beginning and the end of each period. Telmisartan significantly reduced the carotid-femoral PWV compared with placebo (mean adjusted treatment difference -0.95 m/s; 95% CI: -1.67, -0.23 m/s;  $p=0.013$ ). Peripheral and central diastolic, systolic and pulse pressures were also significantly reduced with telmisartan compared with placebo. In conclusion, telmisartan reduces arterial stiffness and peripheral and central BPs as assessed by PWV and pulse contour analysis in hypertensive patients with Type 2 diabetes. These properties of telmisartan suggest that it may improve cardiovascular outcome in this patient population.

### Introduction

Cardiovascular disease is two to three times more common among patients with Type 2 diabetes mellitus than in the general population and it is a major contributor to their increased morbidity and mortality.<sup>1</sup> Hypertension is one of the modifiable risk factors for cardiovascular disease and effective control of blood pressure (BP) in diabetic patients with hypertension can markedly reduce the incidence of cardiovascular events and mortality in this population.<sup>1,3</sup>

Arterial stiffness is an independent risk factor for cardiovascular mortality in hypertensive patients;<sup>3</sup> it is associated with atherosclerosis and is exacerbated in Type 2 diabetes.<sup>4</sup> With vascular stiffening, pulse wave velocity (PWV) increases and the pressure wave characteristics change. This causes the reflected wave to arrive earlier during systole, thus augmenting central systolic BP (SBP) with a consequential increase in pulse pressure

(PP). Such changes are difficult to detect using only conventional sphygmomanometry at the level of the peripheral arteries.<sup>5</sup> In this regard, PWV measurement is widely used as an index of arterial stiffness<sup>4</sup> and pulse wave contour analysis (PWA) is used to calculate central pressures, augmentation and the augmentation index.<sup>6</sup>

Peripheral BP can be reduced by a variety of antihypertensives, but these drugs vary in their effects on the arterial wall. Some  $\beta$ -blockers, for example, do not improve central pressures acutely and are less effective in reducing stiffness than other antihypertensive drugs.<sup>7,8</sup> Angiotensin-converting enzyme inhibitors (ACE-I) can reduce arterial stiffness (as assessed by augmentation index) beyond that expected for BP-lowering alone.<sup>9</sup> The improvements in arterial stiffness observed with ACE-Is may in part be due to direct effects on the arterial wall mediated by angiotensin II (Ang II) acting at its AT<sub>1</sub>-receptor.<sup>10</sup>

Angiotensin receptor blockers (ARB) prevent the binding of Ang II to the AT<sub>1</sub>-receptor, providing a more profound blockade of the renin-angiotensin system than ACE-Is. Therefore, this class may be particularly effective in reducing arterial stiffness and central BP. Telmisartan is an ARB that provides effective 24-hour BP control with once-daily dosing and is well tolerated.<sup>11-18</sup> The aim of this study was to assess the effect of telmisartan on arterial stiffness and central BP in patients with Type 2 diabetes mellitus and hypertension.

### Materials and methods

#### Study design

This was a prospective, double-blind, randomised, placebo-controlled, three-week crossover study with an intermediate placebo period. Following a two-week placebo run-in period, eligible patients underwent baseline assessments and were randomised in a 1:1 ratio to take either telmisartan (40 mg) or placebo once-daily for three weeks. At the end of a second two-week placebo wash out period, patients returned to the clinic for repeat baseline assessments and commencement of the second three-week treatment period taking the alternate study drug. Assessments were repeated at the end of each treatment period. All patients gave written informed consent and the study protocol was approved by the appropriate ethics committee.



### Study population

Patients were aged  $\geq 30$  years and fulfilled the following inclusion criteria: mild-to-moderate essential hypertension (diastolic BP [DBP]  $\geq 85$  mmHg,  $\leq 110$  mmHg); Type 2 diabetes mellitus according to the World Health Organization (WHO) classification;  $HbA_{1c} < 9.0\%$ ; any anti-diabetic therapy should have been stable for at least three months. The major exclusion criteria included the following: severe or secondary hypertension, body mass index  $< 22$  kg/m<sup>2</sup> or  $> 35$  kg/m<sup>2</sup>, severe renal or hepatic impairment, recent cardiovascular disorders, or concomitant use of insulin or medications known to affect BP.

### Study endpoints

The primary efficacy endpoint was the change from baseline in PWV over the carotid-femoral route. Secondary efficacy endpoints included the change from baseline of the following: PWV over the carotid-radial route; central or peripheral SBP, DBP and PP; augmentation index; first and second peak delay and subendocardial viability index.

### Clinical measurements

PWV was determined using an automatic device, the Complior™ (Artech Medical, Paris, France), which allows online pulse wave recording and automatic calculation of PWV.<sup>19</sup> Briefly, the pressure waveforms were recorded simultaneously using specific pressure-sensitive transducers. When the operator observed a pulse waveform of sufficient quality on the computer screen, digitisation was suspended, and calculation of the time delay (t) between the two pressure upstrokes initiated. Measurement was repeated over 12 seconds. The distance travelled by the pulse wave was measured over the body surface as the distance between the two recording sites (D); pulse transit time (t) was determined by the Complior™. PWV was automatically calculated as  $PWV = D/t$ . Validation of this method and its reproducibility have been reported previously.<sup>19</sup>

Pulse contour analysis and central BP measurements were performed using the SphygmoCor™ device (PWV, Sydney, Australia). The pressure wave was recorded at the radial artery using a handheld pencil probe based on applanation tonometry. For BP determinations, brachial and radial BPs were considered equivalent. The device allows calculation of central BP and analysis of the pulse contour with determination of the augmentation index, first and second peak delay and subendocardial viability index. Details of the procedure have been described elsewhere.<sup>20</sup>

### Statistical analysis

Analyses of efficacy were performed on the intention-to-treat (ITT) population, defined as all randomised subjects who had taken at least one dose of study medication. In order for a subject to be included in a particular efficacy analysis, it was necessary for them to have complete data from both treatment periods. The changes from baseline for the PWV and PWA measures and central and periph-

**Table 1** Patient baseline characteristics (intention-to-treat population).

	Telmisartan 40 mg/ placebo (n=13)	Placebo/ telmisartan 40 mg (n=14)	Total (n=27)
Age (years)	62.7 $\pm$ 6.8	62.3 $\pm$ 12.0	62.5 $\pm$ 9.7
Male, n (%)	11 (85)	8 (57)	19 (70)
BMI (kg/m <sup>2</sup> )	27.9 $\pm$ 3.6	28.7 $\pm$ 4.4	28.3 $\pm$ 4.0
Smoker or ex-smoker, n (%)	8 (62)	3 (21)	11 (41)
Alcohol usage, n (%)	8 (62)	2 (14)	10 (37)

Mean $\pm$ standard deviation; BMI: body mass index.

eral pressures were compared between treatments using an analysis of variance, taking into account variation due to subject, treatment period, appropriate baseline value and treatment. An estimate for the treatment difference, with a 95% confidence interval, was produced together with a corresponding p-value. With 24 evaluable subjects, the study was powered at 90% to detect at least a 0.75 m/s difference in the primary variable (PWV carotid-femoral route) between telmisartan and placebo. A test was conducted to assess the presence of carryover effects. Residual checks were performed to verify that the assumptions of the model had been satisfied.

## Results

### Patients

A total of 28 patients were randomised into the study, of which 27 were eligible to be included in the ITT population (13 patients received telmisartan followed by placebo and 14 received placebo followed by telmisartan). Baseline characteristics of the patients are summarised in Table 1. Baseline peripheral SBP/DBP was similar for both treatments (147.6/89.8 mmHg and 149.9/89.7 mmHg for telmisartan and placebo, respectively) as were the baseline central SBP/DBP (140.6/90.7 mmHg and 141.7/90.5 mmHg for telmisartan and placebo respectively). Baseline values for PWV and augmentation index are presented in Table 2.

### Arterial stiffness and pulse wave analysis

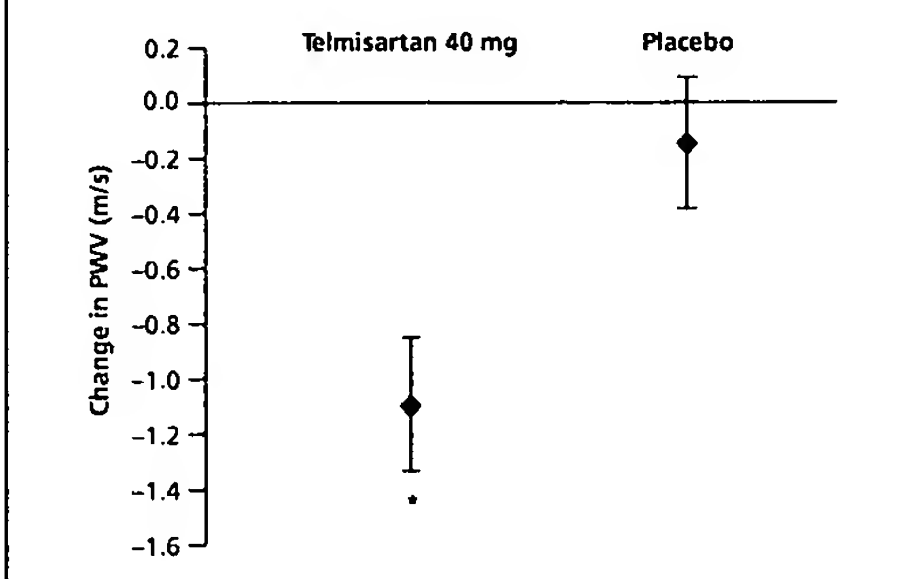
Following treatment for three weeks, telmisartan significantly reduced the PWV over the carotid-femoral route compared with placebo (Figure 1, Table 2). The mean adjusted treatment difference was  $-0.95$  m/s favouring telmisartan (95% CI:  $-1.67$ ,  $-0.23$  m/s;  $p=0.013$ ). Telmisartan also reduced the PWV over the carotid-radial route compared with placebo (Table 2), although the effect was less pronounced. The treatment difference approached statistical significance, with a mean adjusted value of  $-0.64$  m/s in favour of telmisartan (95% CI:  $-1.29$ ,  $0.01$  m/s;  $p=0.052$ ).

With regard to the augmentation index, although telmisartan provided a greater decrease from baseline when compared with placebo

**Table 2** Treatment effect on pulse wave velocity (PWV) and augmentation index (intention-to-treat population).

	Telmisartan 40 mg	Placebo
<b>Carotid-femoral PWV (m/s)</b>		
n	20	20
Baseline, mean±SD	12.53±2.50	13.07±1.84
Adjusted mean change from baseline (95% CI)	-1.096* (-1.596, -0.595)	-0.146 (-0.647, 0.355)
<b>Carotid-radial route PWV (m/s)</b>		
n	22	22
Baseline, mean±SD	10.35±1.77	10.83±1.38
Adjusted mean change from baseline (95% CI)	-0.804 (-1.254, -0.354)	-0.164 (-0.614, 0.287)
<b>Augmentation index (%)</b>		
n	23	23
Baseline, mean±SD	32.2±8.9	28.4±11.9
Adjusted mean change from baseline (95% CI)	-2.9 (-5.3, -0.4)	0.2 (-2.2, 2.7)

Telmisartan versus placebo \*p≤0.05.

**Figure 1** Adjusted mean changes from baseline (±SEM) in pulse wave velocity (PWV; carotid-femoral route) after three weeks of treatment with telmisartan 40 mg or placebo. \*p=0.013 (intention-to-treat population).

(Table 2), the mean adjusted treatment difference of -3.1% (95% CI: -6.6, 0.5%), did not achieve statistical significance (p=0.09). Results of the effect of telmisartan on other secondary pulse wave analyses (Table 3) were not significantly different from placebo.

### Blood pressure

Compared with placebo, telmisartan produced significant decreases in central and peripheral DBP, SBP and PP (Figure 2, Table 4). Interestingly, the effect of telmisartan on BP in peripheral arteries was very similar to that seen in central arteries.

### Discussion

Arterial stiffness increases with age<sup>21</sup> and is exacerbated by hypertension.<sup>22</sup> In patients with diabetes mellitus, arterial stiffness is accelerated and present even in the early stages of the disease.<sup>23-25</sup> Patients with diabetes also often have atherosclerosis and hypertension and are predisposed to cardiovascular disease.

An increase in arterial stiffness leads to an increase in PWV and to a decrease in the ability of the arteries to buffer the pressure wave. One consequence of this arterial alteration is an increase in the amplitude and early return of the reflected

**Table 3** Secondary variables from pulse wave analysis. Results are expressed as the mean change from baseline after three weeks on treatment (intention-to-treat population).

	Telmisartan 40 mg	Placebo
Ejection duration (%)	-8.3±13.4	-0.3±22
First peak delay (ms)	2.9±12.2	2.3±9.0
Second peak delay (ms)	-10.2±19.2	3.4±15.7
Subendocardial viability (%)	1.4±17.1	4.4±16.8

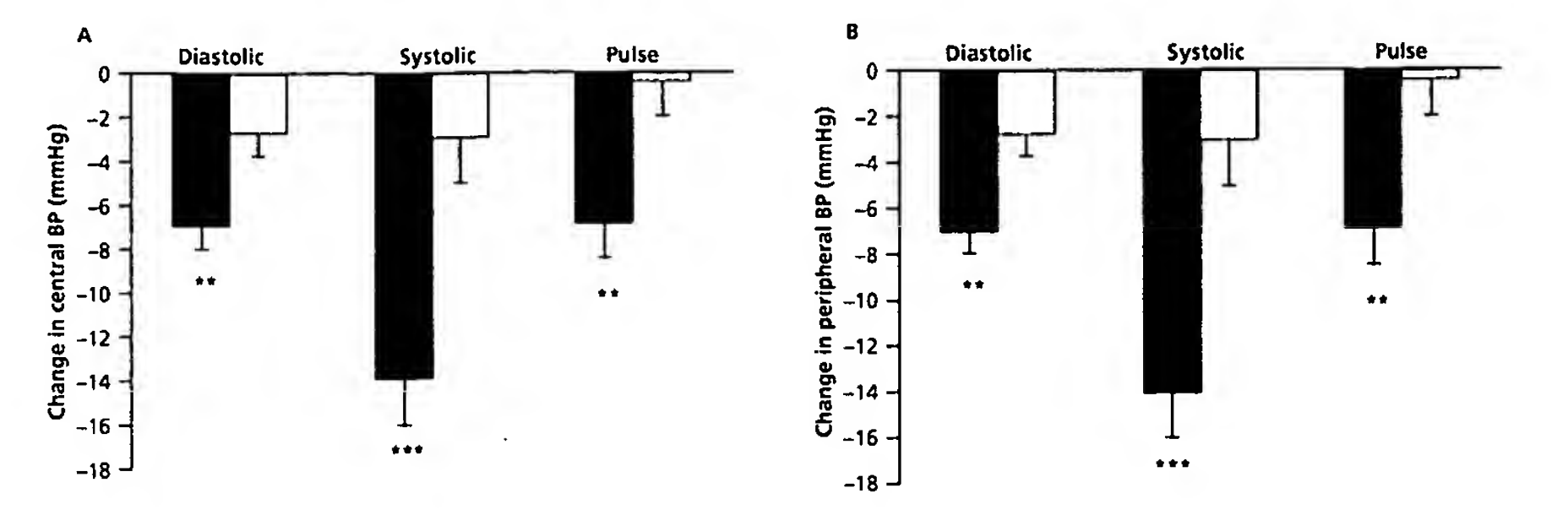
Mean change from baseline±SD.

pressure wave with augmentation of central SBP and PP. Increased SBP leads to left ventricular hypertrophy and is an important predictor of cardiovascular risk.<sup>26-28</sup> However, there is also increasing evidence that elevation of PP, rather than SBP or DBP alone, is an important independent predictor of cardiovascular risk.<sup>29-32</sup> Recently, Franklin<sup>33</sup> studied normotensive and untreated hypertensive patients over a 20-year period in a population-based cohort from the Framingham Heart Study. PP was found to be superior to DBP and SBP as a marker of both arterial stiffness and also the risk of coronary heart disease. These findings highlight the importance of arterial stiffness as a marker of cardiovascular disease.<sup>29,30</sup>

Direct evidence of the role of arterial stiffness in cardiovascular morbidity has been demonstrated by Blacher *et al.*,<sup>34</sup> and more recently by Laurent *et al.*,<sup>3</sup> who have shown that arterial stiffness, as evaluated by PWV, is an independent predictor of cardiovascular and all-cause mortality in hypertensive patients.

The results of the present study showed that PWV (carotid-femoral route) was significantly reduced after three weeks of treatment with telmisartan compared with placebo. Additionally, PWV measured via the carotid-radial route was also reduced by telmisartan and approached statistical significance over placebo. These findings may reflect the different physical characteristics of the two vessels: the aorta is relatively more

**Figure 2** Adjusted mean effects of telmisartan 40 mg (filled bars) compared with adjusted mean effects placebo (unfilled bars) on central (A) and peripheral (B) diastolic, systolic and pulse pressures (intention-to-treat population). Error bars show standard errors. Telmisartan 40 mg significantly reduced central and peripheral blood pressures (BPs) compared with placebo. \*\* $p \leq 0.01$ , \*\*\* $p \leq 0.001$ .



**Table 4** Treatment effect of telmisartan 40 mg compared with placebo on central and peripheral systolic (SBP), diastolic (DBP) and pulse pressures (PP) after three weeks (intention-to-treat population).

	SBP	DBP	PP
<b>Central blood pressure, (mmHg)</b>			
Adjusted mean difference	-11.0	-4.5	-6.4
95% CI	-16.8, -5.3	-7.6, -1.3	-10.8, -2.0
p-value	p=0.001	p=0.008	p=0.006
<b>Peripheral blood pressure, (mmHg)</b>			
Adjusted mean difference	-11.1	-4.3	-6.5
95% CI	-17.0, -5.1	-7.4, -1.3	-11.2, -1.8
p-value	p=0.001	p=0.008	p=0.009

n=23 for both telmisartan 40 mg and placebo groups.

elastic than the radial artery, which is more muscular, so treatment effects on arterial wall distensibility may be less obvious. The associated augmentation index, which indicates the effect of early wave reflection on central SBP, was also reduced by telmisartan, although this reduction did not reach statistical significance.

As expected, compared with placebo, telmisartan significantly reduced peripheral DBP and SBP. However, it is of interest to note that telmisartan also provided similar significant decreases in central BPs. The beneficial effect of peripheral DBP and SBP control in the prevention of cardiovascular events has been widely studied.<sup>35</sup> With regard to patients with diabetes mellitus, the Hypertension Optimal Treatment (HOT) study<sup>36</sup> demonstrated that intensive BP control was particularly beneficial in the diabetic subgroup. Similarly, the UK Prospective Diabetes Study (UKPDS)<sup>1</sup> showed that tight control of peripheral BP halved the incidence of stroke and heart failure.

Telmisartan also significantly reduced PP to a similar degree in both peripheral and central arteries. This is a notable finding, owing to the importance of PP as a cardiovascular risk factor. The pathophysiological consequences of widening PP result from effects in central rather than peripheral arteries. However, the importance of central pressures in this regard is not widely recognised

and treatment is targeted against peripheral BP.<sup>37</sup> Certainly, peripheral BP changes induced by some antihypertensive agents may be smaller than those achieved centrally,<sup>38</sup> and alone may not be fully representative of the beneficial effects of treatment on larger arteries. In this regard, the significant decreases in central as well as peripheral DBP, SBP and PP found with telmisartan are interesting and are not inconsistent with findings for some ACE-Is.<sup>39-41</sup> The possibilities represented by combining an ACE-I with an ARB are even more intriguing.<sup>42</sup>

In conclusion, assessment of PWV in conjunction with central PP can provide additional useful information on the efficacy of antihypertensive therapies, particularly since increased arterial stiffness and widening PP are associated with end-organ damage and are independent predictors of cardiovascular risk. An antihypertensive agent that can significantly reduce arterial stiffness and improve both central and peripheral PP may potentially provide greater beneficial effects on cardiovascular outcomes, beyond that seen with BP-lowering alone. Telmisartan reduced arterial stiffness, as indicated by carotid-femoral PWV, and significantly improved central and peripheral DBP, SBP and PP in hypertensive patients with Type 2 diabetes. Whether telmisartan can influence cardiovascular outcomes beyond BP control warrants further investigation in clinical studies.



## Acknowledgements

This study was sponsored by GlaxoSmithKline Research and Development, UK. We thank Ruby Terracciano for writing and editing assistance. The authors thank the investigators and their co-workers for their contribution to this study, Sally Gray and Lisa Williams, GlaxoSmithKline R&D, UK.

## References

- King P, Peacock I, Donnelly R. The UK Prospective Diabetes Study (UKPDS): clinical and therapeutic implications for Type 2 diabetes. *Br J Clin Pharmacol* 1999;48:643-8.
- Joint National Committee on Prevention, Detection, Evaluation, Treatment of High Blood Pressure. The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med* 1997;157:2413-46.
- Laurent S, Boutouyrie P, Asmar R *et al*. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension* 2001;37:1236-41.
- Asmar R. Arterial Stiffness and Pulse Wave Velocity. In: *Pulse wave velocity and prognosis*. Paris: Elsevier; 1999; 93-9.
- O'Rourke MF. Arterial mechanics and wave reflection with antihypertensive therapy. *J Hypertens* 1992;10(suppl 5):S43-9.
- O'Rourke MF, Gallagher DE. Pulse wave analysis. *J Hypertens* 1996;14(suppl 5):S147-57.
- O'Rourke MF, Kelly RP, Avolio AP, Hayward C. Effects of arterial dilator agents on central aortic systolic pressure and on left ventricular hydraulic load. *Am J Cardiol* 1989;63:381-441.
- Safar ME. Pulse pressure in essential hypertension: clinical and therapeutic implications. *J Hypertens* 1989;7:769-76.
- Chen CH, Ting C-T, Lin S-J *et al*. Different effects of fosinopril and atenolol on wave reflections in hypertensive patients. *Hypertension* 1995;25:1034-41.
- Benetos A, Levy BI, Lacolley P, Taillard F, Duriez M, Safar ME. Role of angiotensin II and bradykinin on aortic collagen following converting enzyme inhibition in spontaneously hypertensive rats. *Arterioscler Thromb Vasc Biol* 1997;17:3196-201.
- Neutel JM, Smith DHG. Dose response and antihypertensive efficacy of the AT1 receptor antagonist telmisartan in patients with mild to moderate hypertension. *Adv Ther* 1998;15:206-17.
- Smith DHG, Neutel JM, Morgenstern P. Once-daily telmisartan compared with enalapril in the treatment of hypertension. *Adv Ther* 1998;15:229-40.
- Lacourcière Y, Lenis J, Orchard R *et al*. A comparison of the efficacy and duration of action of the angiotensin II receptor blocker telmisartan to amlodipine. *Blood Press Monit* 1998;3:295-302.
- Neutel JM, Frishman WH, Oparil S, Papademitriou V, Guthrie G. Comparison of telmisartan with lisinopril in patients with mild-to-moderate hypertension. *Am J Ther* 1999;6:161-6.
- Mallion JM, Siché JP, Lacourcière Y, the Telmisartan Blood Pressure Monitoring Group. ABPM comparison of the antihypertensive profiles of the selective angiotensin II receptor antagonists telmisartan and losartan in patients with mild-to-moderate hypertension. *J Hum Hypertens* 1999;13:657-64.
- Lacourcière Y, the Telmisartan Cough Study Group. The incidence of cough: a comparison of lisinopril, placebo and telmisartan, a novel angiotensin II antagonist. *Int J Clin Pract* 1999;53:99-103.
- Karlberg BE, Lins L-E, Hermansson K, for the TEES Study Group. Efficacy and safety of telmisartan, a selective AT1 receptor antagonist, compared with enalapril in elderly patients with primary hypertension. *J Hypertens* 1999;17:293-302.
- Sharpe M, Jarvis B, Goa KL. Telmisartan: a review of its use in hypertension. *Drugs* 2001;61:1501-29.
- Asmar R, Topouchian J, Pannier B, Benetos A, Safar M. Pulse wave velocity as endpoint in large-scale intervention trial. The Complior study. Scientific, Quality Control, Coordination and Investigation Committees of the Complior Study. *J Hypertens* 2001;19:813-18.
- Nichols WW, O'Rourke MF (eds.). *MacDonald's blood flow in arteries. Theoretical, experimental and clinical principles*. 4th ed. London: Edward Arnold, 1998;54-113, 201-22, 84-92, 347-401.
- Avolio AP, Chen SG, Wang RP, Zhang CL, Li MF, O'Rourke MF. Effects of aging on changing arterial compliance and left ventricular load in a northern Chinese urban community. *Circulation* 1983;68:50-8.
- Asmar R, Benetos A, London G *et al*. Aortic distensibility in normotensive, untreated and treated hypertensive patients. *Blood Press* 1995;4:48-54.
- Lehmann ED, Gosling RG, Sonksen PH. Arterial wall compliance in diabetes. *Diabet Med* 1992;9:114-19.
- Glasser SP, Arnett DK, McVeigh GE *et al*. Vascular compliance and cardiovascular disease: a risk factor or a marker? *Am J Hypertens* 1997;10:1175-89.
- Brooks B, Molyneaux L, Yue DK. Augmentation of central arterial pressure in Type 1 diabetes. *Diabetes Care* 1999;22:1722-7.
- Gosse P, Jullien V, Jarnier P, Lemetayer P, Clementy J. Reduction in arterial distensibility in hypertensive patients as evaluated by ambulatory measurement of the QKD interval is correlated with concentric remodeling of the left ventricle. *Am J Hypertens* 1999;12:1252-5.
- Wilkinson IB, MacCallum H, Rooijmans DF *et al*. Increased augmentation index and systolic stress in Type 1 diabetes mellitus. *QJM* 2000;93:441-8.
- Benetos A, Laurent S, Asmar RG, Lacolley P. Large artery stiffness in hypertension. *J Hypertens* 1997;15(suppl 2):S89-97.
- Benetos A, Safar M, Rudnichi A *et al*. Pulse pressure: a predictor of long-term cardiovascular mortality in a French male population. *Hypertension* 1997;30:1410-15.
- Franklin SS, Khan SA, Wong ND, Larson MG, Levy D. Is pulse pressure useful in predicting risk for coronary heart disease? The Framingham heart study. *Circulation* 1999;100:354-60.
- Madhavan S, Ooi WL, Cohen H, Alderman MH. Relation of pulse pressure and blood pressure reduction to the incidence of myocardial infarction. *Hypertension* 1994;23:395-401.
- Blacher J, Staessen JA, Girerd X *et al*. Pulse pressure not mean pressure determines cardiovascular risk in older hypertensive patients. *Arch Intern Med* 2000;160:1085-9.
- Franklin SS. Ageing and hypertension: the assessment of blood pressure indices in predicting coronary heart disease. *J Hypertens* 1999;17(suppl 5):S29-36.
- Blacher J, Asmar R, Djane S, London GM, Safar ME. Aortic pulse wave velocity as a marker of cardiovascular risk in hypertensive patients. *Hypertension* 1999;33:1111-17.
- Collins R, MacMahon S. Blood pressure, antihypertensive drug treatment and the risks of stroke and of coronary heart disease. *Br Med Bull* 1994;50:272-98.
- Hansson L, Zanchetti A, Carruthers SG *et al*. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *Lancet* 1998;351:1755-62.
- Karamanoglu M, O'Rourke MF, Avolio AP, Kelly RP. An analysis of the relationship between central aortic and peripheral upper limb pressure waves in man. *Eur Heart J* 1993;14:160-7.
- Franklin SS. New interpretations of blood pressure: the importance of pulse pressure. In: Oparil S, Weber MA (eds.). *Hypertension: a companion to Brenner and Rector's The Kidney*. Philadelphia: W.B. Saunders Company, 2000;227-34.
- Dart AM, Reid CM, McGrath B, on behalf of the Tonometry Study Group. Effects of ACE inhibitor therapy on derived central arterial waveforms in hypertension. *Am J Hypertens* 2001;14:804-10.
- Pannier BM, Guerin AP, Marchais SJ, London GM. Different aortic reflection wave responses following long-term Angiotensin-converting enzyme inhibition and Beta-blocker in essential hypertension. *Clin Exp Pharmacol Physiol* 2001;28:1074-7.
- Asmar RG, London GM, O'Rourke ME, Safar ME, and the REASON Project Coordinators and Investigators. Improvement in blood pressure, arterial stiffness and wave reflections with a very-low-dose perindopril/indapamide combination in hypertensive patient: a comparison with atenolol. *Hypertension* 2001;38:922-6.
- Mahmud A, Feely J. Favourable effects on arterial wave reflection and pulse pressure amplification of adding angiotensin II receptor blockade in resistant hypertension. *J Hum Hypertens* 2000;14:541-6.